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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
O DELL, DAVID K	
ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/511,319	BAN ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *21 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☒ Claim(s) *18-20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :15 October 2004, 06 December 2004, 05 December 2005 .

DETAILED ACTION

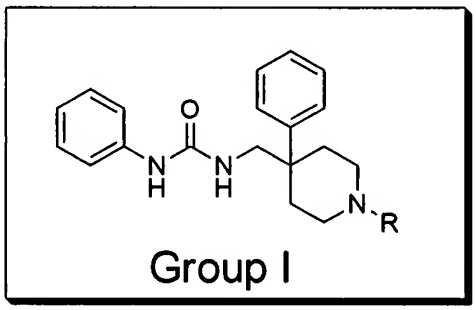
1. Claims 1-22 are pending in the current application. Claims 1-20 are under examination. Claims 20-22 are withdrawn from consideration.

2. This application is a national stage of PCT/JP03/05124 filed April 22, 2003, which claims priority to Japanese application 2002124311 filed April 25, 2002.

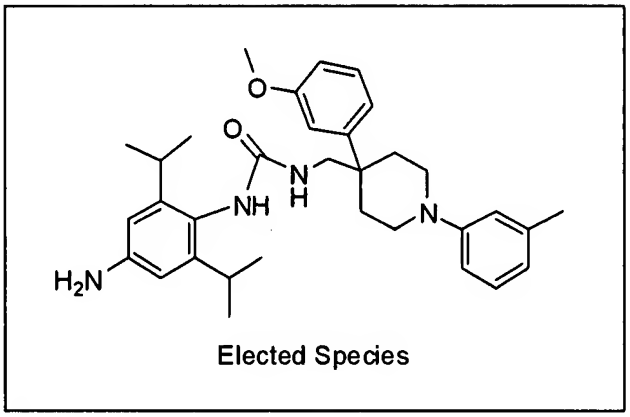
Response to Restriction/Election

3. Applicant's election without traverse of Group I and the species of Example 12-2 (i.e., N-{[1-(3-methyl-phenyl)-4-(3-methoxyphenyl)piperidin-4-yl]methyl}-N'-(4-amino-2,6-diisopropylphenyl)urea), in the reply filed on August 16, 2007 is acknowledged. This requirement is made FINAL. This application contains claims drawn to a nonelected invention. A complete reply to this action must include a cancellation of nonelected claims or other appropriate action.

Group I, claims 1-20 drawn to piperidinyl ureas, where m=2, n =2, R31=R32=R33=R34=R35=R36=H, Y=phenyl, L=phenyl, R=alkyl (including benzyl), phenyl or pyridyl as shown in the figure below. If this group is elected, a further election of a single disclosed species is also required.



Group I



Elected Species

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In addition to being drawn to a non-elected invention, the claims are incomprehensible with variables nested inside variables nested inside variables. These matryoshka claims make it difficult to ascertain what is actually being claimed. Some unusual groups represent no actual groups: O-E-A can be O and E can be C1-alkyl optionally containing an "unsaturated bond". Is this a methyl group containing a double bond? Is this an oxocarbenium ion? What is this group? Other examples of substituents that have no definite meaning include as in claim 8 "carboxyl group", "alkoxycarbonyl" these terms have no meaning. The term "carbonyl" is for a functional group however carbonyl can be a portion of an amide, acid, ester, aldehyde, ketone, metal carbonyl, etc. and can encompass compounds of an indefinite scope and as written has a dangling valance (See Ex Parte Diamond (POBA 1959) 123 USPQ

167). What is the point of attachment to the molecule of these groups for example is a "heteroarylmethyl" group bonded through the heteroaryl ring or the methyl group? The term "substituted" renders all the claims indefinite. Unless one knows what a substituent is a determination of what these compounds are cannot be made. The specification does not fully elaborate the identity of these substituents. This rejection is not being made for breadth, which will be discussed at length in this action at 7 (pg. 5). The specification states on pg. 10:

> "The substituted alkyl group, the substituted alkenyl group, and the substituted alkynyl group **may have one or more substituents which are the same or different, and the substituents are, for example,** a **substituted or unsubstituted aromatic group, a substituted or unsubstituted cycloalkyl group**, a halogen atom, a cyano group, a....." (Emphasis added).

See MPEP 2173.05(d), for the use of exemplary language ("for example"). The defining of substituents as being substituted with groups that are further "substituted" with unknown substituents causes even further ambiguity and indefiniteness. This definition is repeated throughout the claims and the specification redefines each group in this ambiguous manner. The claims also use the language if "R35 and R36....if both exist". What does this mean? How can they not exist? Does this imply that carbene is being claimed if they don't exist?

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

5. Claims 1-3, 17-20 are rejected under 35 U.S.C. 102(a) as being anticipated by Hobbs et. al. WO 02/083134 A1 (cited by applicant on IDS). Hobbs discloses a hundred or so compounds that anticipate the instant claims. Table 1 pgs 59-88 reveals the compounds where m=2, n =2, R31=R32=R33=R34=R35=R36=H, Y=phenyl (substituted variously), L=phenyl (substituted variously), R=alkyl (substituted variously), that meet the instant claims.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1-3, 17-20 are rejected under 35 U.S.C. 102(e) as being anticipated by Hobbs et. al. U. S. Pre-grant Publication 2003/0013720 now U.S. patent 6,887,889 B2, which has the same disclosure as the WIPO document of the 102(a) rejection (supra), hence the rejection has the same basis (i.e. Table 1).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compounds does not reasonably provide enablement for the protracted list of compounds bearing the protracted list of substituents. The compounds that are enabled for synthesis are as follows:

R is pyridyl, phenyl, benzyl, alkyl, which may be substituted with alkoxy, alkyl, chloro, trigfluormethyl, alkyl; L of Formula 2 (claim 4), where R3, R4 and Z are in claim 4, Y is phenyl

substituted with alkoxy, benzyloxy, hydroxy, fluoro, trifluoromethyl, and no substituents on the piperidine ring, or the methylene alpha to the ring (i.e.. R31=R32=R33=R34=R35=R36=H) The guidance on how to use as been provided for only three compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

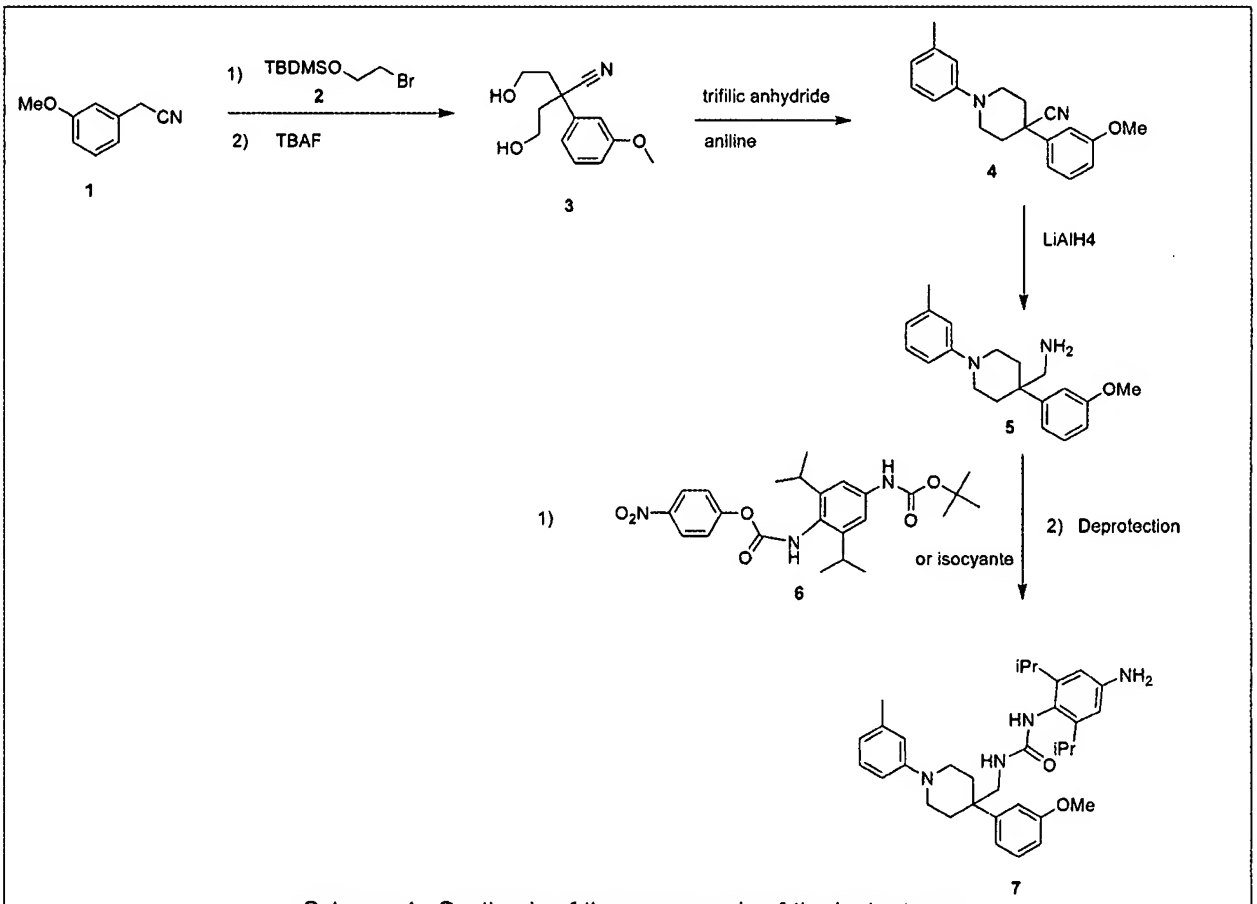
(A) The breadth of the claims: The claims are very broad encompassing a variety of heterocycles, carbocycles and other groups bearing multiple substitutions of unknown identity (hence the 112 2nd rejection for "substituted") **(B) The nature of the invention:** This is a chemical invention requiring the synthesis of compounds and such compounds should have inhibitory activity at ACAT. **(D) The level of one of ordinary skill**: One of ordinary skill is a practicing organic/medicinal chemist. Chemistry is unpredictable. See In Re Marzocchi and Horton 169 USPQ at 367 paragraph 3. **(C) The state of the prior art: (E) The level of predictability in the art: (F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention:** Each one of the factors (**C, E-H**) will be discussed in light of the scientific

literature when such a factor is being directly pointed to a large capital letter referring to the aforementioned Wands factor will be placed directly after such a remark or explication. The examiner will first consider the Markush structure 1 of claim 1, and discuss the limitations inherent to the paucity of available starting materials, as well as the inherent limitations of the chemistry used to prepare the examples.

As per MPEP:

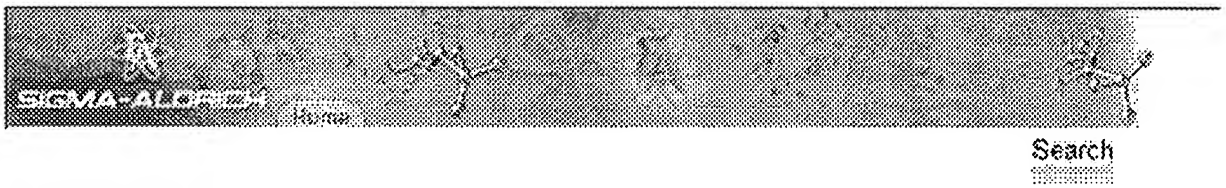
> A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court in In re Ghiron, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can be said if certain chemicals are required to make a compound or practice a chemical process. In re Howarth, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

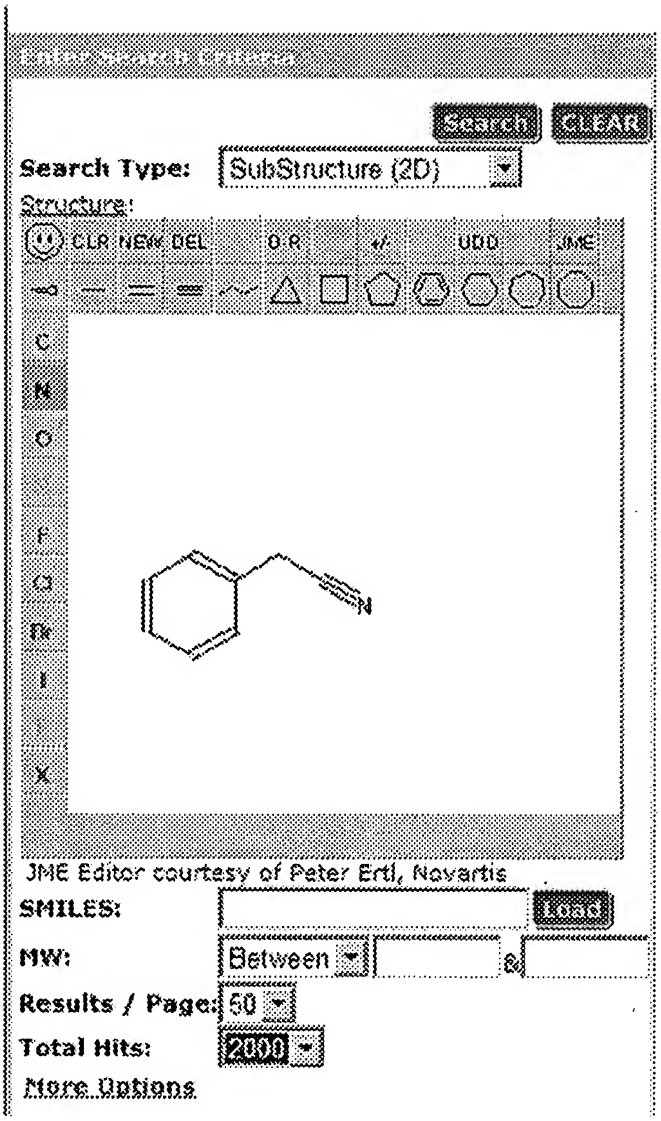
The synthesis given in the specification is shown in Scheme 1.



Scheme 1. Synthesis of the compounds of the instant case.

Based on the synthesis given one that is given double alkylation of a benzylic anion, one would need an infinite number of 1-bromo-2-siloxyethanes (**2**) in order to support all these subsituents, a search for these materials reveals none **(C)**. The situation for benzylic nitriles **1** is similar and a search of the Sigma-Aldrich catalog reveals only very modest substitution (see Substructure Search, attached), such as halogen, methoxy, nitro, hydroxy, and alkyl as being available, since both benzylic hydrogen atoms must be available.





According to the U.S. Court of Customs and Patent Appeals in *In re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 101, "[o]rdinarily no problem in this regard arises since the method of preparing almost all starting materials can be set forth in writing if the materials are not already known and available to the workers in the art, and when this is done the specification is enabling

to the public". *In re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 104, "it is essential that there be no question that, *at the time an application for patent is filed,* (emphasis in original) the invention claimed therein is fully capable of being reduced to practice (i.e., that no technological problems, the resolution of which would require more than ordinary skill and reasonable time, remain in order to obtain an operative, useful embodiment)." That is not the situation here. Rather we find very little direction as to how the many required staring materials required for the synthesis of these benzylnitrile **1**, or-bromo-2-siloxyethanes **2** are to be obtained **(F)**. Where may the directions to prepare or buy them be found?

In re Howarth, 210 USPQ 689, (claimed derivatives of clavulanic acid not enabled by specification lacking information of how prepare the clavulanic acid or directions to reference materials containing such information), *Ex parte Schwarze* 151 USPQ 426 (where starting material is not known to art as of date of filing application, there must be included a description of preparation thereof to enable one skilled in this art to carry out applicant's invention), *Ex parte Moersch* 104 USPQ 122 (claims to process for the production of (1)-yl-p-nitrophenyl-2-dichloracetamindo-propane-1,3-diol not enabled because of failure to describe source or method of obtaining starting compound; although starting compound is identified by means of appropriate name and by structural formula). Genetech Inc Vs Nova Nordisk 42 USPQ 2d 1001 "A patent is not a hunting license. It is not a reward for search but compensation for its successful conclusion and patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

The limitations of the chemistry used to prepare the compounds is readily apparent as stated in the preface to a recent treatise:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work.....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious)....." Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface. **(E)**

A key step in the formation of all the piperidine subunit is the bis-alkylation of aniline of with triflates (as in **3** to **4**) **(F & G)** however these reactions are very sensitive to the structure of the aniline **(C & E)**. In fact, as stated by Dorwald ibid. pg. 236-237 "The close proximity of functional groups in 1,2-disubstituted benzenes can sometimes bring about an unexpected

reactivity. Attempts to N-alkylate ortho-nitroanilines under strongly basic reaction conditions, for instance lead to the formation of N-alkoxybenzimidazoles (Scheme 6.10). ...haloalkylamines are problematic reagents will readily polymerize or cyclize under basic conditions.....Reactions of this type will only proceed well with electron-rich nucleophillic anilines, but fail with electron-deficient anilines... " **(C & E)** Of course the presences of multiple nucleophiles can be problematic, (although it is clear that hydroxy is enabled since conditions are given for demthylation of the product) Many of the compounds currently under the Markush claim could not exist but would self-polymerize instantaneously if prepared as stated by Dorwald ibid. pg. 41 "It goes without saying that a compound will decompose or oligomerize if it contains functional groups which can react with each other. Because intramolecular reactions often proceed at much higher rates than their intermolecular variants, functional group incompatibilities may arise unexpectedly, involving groups which would not react intermolecularly..." **(C & E)** The R35 and R36 come from the reduction of a nitrile with LiAlH4, Thus the H atoms here originate from LiAlH4. Is the applicant preparing new organometallics that can transfer alkyl groups to nitriles or convert the nitrile carbon to an oxo group? The list of reagents that are incompatable with "substituents" could be discussed at length for perhaps weeks given the scope of the claims. Consider $LiAlH_4$ (Scheme E), a very promiscuous reductant indeed that will react with nearly any electrophilic functional group ("Lithium Aluminum Hydride" Paquette, L. in *Encyclopedia of Reagents for Organic Synthesis* Online Posting Date: October 15, 2004 2004 John Wiley & Sons, Ltd. "http://www.mrw.interscience.wiley.com/eros/articles/rl036/frame.html")

While these chemical limitations are significant, perhaps more significantly are the limitations of activity at ACAT. The medicinal chemistry of ACAT is relatively well-developed

and many limitations are well known in the art. These compounds are simply piperidine analogs of known ligands that are very sensitive to structural effects. Trivedi, et. al. "Inhibitors of acyl-CoA:cholesterol acyltransferase. 4. A novel series of urea ACAT inhibitors as potential hypocholesterolemic agents." *Journal of Medicinal Chemistry* **1993**, *36*, 3300 – 3307, has described the SAR in particular with reference to what in this case corresponds to the substituents on L:.

:

> "However, dialkyl substitution in the β-position (17) improved the ACAT inhibitory activity significantly compared to the corresponding apdisubstituted analog 16, suggesting that steric crowding near the urea moiety was disfavored for optimal interaction at the enzyme site. On the basis of these observations, we synthesized a series of j3,Bdialkyl substituted analogs. The in vitro ACAT inhibitory activity was excellent for this series of compounds (17-21). **However, there is a limit to the increase in size or lipophilicity in this part of the molecule, as exemplified by compound 22**. Encouraged by this data, we synthesized and evaluated a series of spirocyclic analogs (Table 11) (23-31). These analogs maintained the in vitro potency of the corresponding acyclic analogs. Additionally, ACAT inhibitory activity was independent of the size of the spirocycle (23-26). The pyridyl analog 27, having a basic nitrogen, was more than 5-fold less active than the corresponding phenyl analog (23), whereas the thienyl analogs (28,29) were equipotent. Once again it is important to note that the "extended" 2-naphthyl analog 30 was significantly less active than the corresponding 1-naphthyl derivative 31.
>
> To confirm whether a 2,6-diisopropyl substituent was also optimal for this series of ACAT inhibitors, we systematically evaluated the effect of mono-, di-, and trisubstitution on the N-phenyl ring. In the series of spirocyclohexyl analogs, substituents such as methoxy (331, methyl (34), isopropyl (351, and trifluoromethyl (36) in the ortho position improved the ACAT inhibitory

activity compared to the unsubstituted analog 32. **However, the polar carboethoxy substituent in the ortho position (37) was deleterious toward activity.** It is the only group capable of forming an internal hydrogen bond with the urea function. This leads to a planar orientation of the urea group with respect to the phenyl ring rendering the compound less active. **Substitution in the meta or para position (38-45) did not improve the activity of the parent compound 32.** A series of disubstituted analogs (46-53) confirmed the preference for 2,6-substitution (51,52) for enhanced potency. The 2,6-bis(dimethylamino) analog (52) was evaluated as a surrogate of 2,6-diisopropyl functionality. Although compound 52 demonstrated good in vitro activity, it was less active than the corresponding 2,6-diisopropyl analog 25 In order to further establish the steric effects of the 2,6-substituents, we prepared the analogs shown in Table IV. Increasing the size of the alkyl substituents not only improved the ACAT inhibitory activity in vitro but also tended to improve cholesterol lowering activity in vivo. The enhancement of both in vitro and in vivo activity was similar for the spirocyclopentyl and spirocyclohexyl analogs. Unsymmetrical substitution (62-67) also rendered the compounds highly potent both in vitro and in vivo. **Thus, this data suggests that for optimal interactions at the active site of the enzyme, a certain spatial arrangement of the requisite carbonyl moiety is necessary, which is achieved by having a bulky 2,6-disubstituent on the phenyl ring**.
" pg. 3301-3302 **(C & E)**

We have not been given any information in regard to the molecular determinants of receptor affinity for the compounds of the instant case. **(F & G)** In fact the only information we are given is the assays for three compounds. What are the important structural features for the claimed utility? We know from Trivedi et. al. certain limitations on R3 and R4 in particular, as well as the size of the piperidine and Y substitutents exist; **(H)** As one reviewer stated, Martin, Yvonne C. et. al. "Do Structurally Similar Molecules Have Similar Biological Activity?" *Journal of Medicinal Chemistry* **2002**, *45*, 4350-4358:

> "..... compounds that look very similar to a chemist sometimes bind in very different orientations in the protein active site, bind to a different conformation of a protein, or bind to a different protein altogether.[15] In fact, such observations are why medicinal chemists need to make so many compounds to optimize the biological activity of a structural class, even when they are designing to a biological target of known structure...(pg. 4536 column 2, line 9).....This work also shows that the biological similarity is not so strong as has previously been assumed. For example, at ≥ 0.85 Tanimoto similarity in Daylight fingerprints, **only 30% of compounds similar to an active are themselves active**."(conclusions) **(H).**

The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a): "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification , at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this very broad invention that has no working examples in this unpredictable art without undue experimentation. **(C, E, F, G, H).**

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 18-20 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are drawn to

"pharmaceutical", "acyl-CoA:cholesterol acyl transferase (ACAT) inhibitor", "agent for the treatment of hyperlipidemia or atherosclerosis", compositions, however no compound has been found to be a pharmaceutical. Since this assertion is contrary to what is known in medicine, proof must be provided that this assertion has merits. Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the "pharmaceutical" use of the instant compounds. Moreover the specification does not seem discloses that only 3 of these compounds inhibit ACAT.

14. Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making prodrugs of the claimed compounds. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental

science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be clinically effective. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

b) The direction concerning the prodrugs is found nowhere in the specification c) There is no working example of a prodrug of a compound the formula I. d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. e) Wolff (Medicinal Chemistry) summarizes the state of the prodrug art. Wolff, Manfred E. "Burger's Medicinal Chemistry, 5ed, Part I", John Wiley & Sons, 1995, pages 975-977. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) Banker, G.S. et al, "Modern Pharmaceutics, 3ed.", Marcel Dekker, New York, 1996, pages 451 and 596. in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. f) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience. g) It is well established that "the scope of enablement varies inversely with the degree of

unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula of claim 1 as well as the presently unknown list of potential prodrug derivatives embraced by other claims.

MPEP 2164.01(a) states, "[a] conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to determine if any particular unknown compound is, in fact, a prodrug.

Nowhere in the specification are directions given for preparing the "prodrugs" of the claimed compounds. Since the structures of these "prodrugs" are uncertain, direction for their preparation must also be unclear. Directions to a team of synthetic pharmaceutical chemists and metabolism experts of how to search for a "prodrug" hardly constitute instructions to the BS process chemist of how to make such a compound.

Objections

8. The disclosure is objected to because of the following informalities: the term "benzhydrile" is used throughout the specification this should be "benzhydryl".

Appropriate correction is required.

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

The specification appears to be coming from some other format with headings entitled "Experiments" "Backgroun Art"[sic], "Industrial Applicability", "Best mode for carrying out the invention" etc....

9. Claims 18-20 are objected to because of the following reasons: They are drawn to compounds and compositions, despite the recitation of functional language "pharmaceutical", "acyl-CoA:cholesterol acyl transferase (ACAT) inhibitor", "agent for the treatment of

hyperlipidemia or atherosclerosis", they are drawn to the same materials. Functional language as that of the instant claims carries no patentable weight in claims for compositions of matter see *Union Oil Co. of California v. Atlantic Richfield Co.* 54 USPQ2d 1227 where "composition claims cannot, as the appellant refiners argue, embrace only certain uses of that composition. (citing In Re Spada) Otherwise these composition claims would mutate into method claims." It is recommended that claims 19 and 20 be canceled and claim 18 be rewritten to recite "composition" without intended use by simply removing the term pharmaceutical.

Conclusion

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571) 272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

11. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Primary examiner, Rita Desai can be reached on (571)272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

RDesai 8/31/07

RITA DESAI
PRIMARY EXAMINER